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Impact of anti-SARS-CoV-2 monoclonal antibodies in the management of patients with lymphoma and COVID19: A retrospective study

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Abstract

COVID19 in patients affected by lymphoma represents an important challenge because of the higher mortality rate. Anti-SARS-CoV-2 monoclonal antibodies (anti-S MoAbs) appear promising in this setting. We report a monocentric retrospective study including 176 patients affected by lymphoma which developed SARS-CoV-2 infection since the start of COVID19 pandemic. Overall, mortality was 13.1%, with a decreasing trend between first waves to the last wave of pandemic (18.5% vs. 9.4%, *p* 0.076). Patients receiving anti-S MoAbs (41.3%) showed inferior mortality rate (overall survival, OS 93.2% vs. 82.7%, *p* 0.025) with no serious toxicity, reduced documented pneumonia (26% vs. 33%, *p* 0.005), and reduced need of oxygen support (14.5% vs. 35.7%, *p* 0.003). Among patients who received 3 doses of vaccine, the employment of anti-COVID MoAbs showed a trend of superior survival versus those who did not receive Anti-S MoAbs (OS rates 97.3% vs. 84.2%, *p* 0.064). On multivariate analysis, active haematological disease (OS 72% (HR 2.49 CI 1.00–6.41), bendamustine exposure (OS 60% HR 4.2 CI 1.69–10.45) and at least one comorbidity (HR 6.53 CI 1.88–22.60) were independent prognostic factors for death. Our study confirms the adverse prognostic role of COVID-19 in lymphoma patients in presence of active disease, comorbidities and previous exposure to bendamustine. In our experience, anti-S MoAbs represented a therapeutic option in vaccinated patients.

KEYWORDS
bendamustine, COVID-19, lymphoma, monoclonal antibodies, non hodgkin lymphoma

Giovanni Manfredi Assanto and Alice Di Rocco contributed equally to this work

1 | INTRODUCTION

Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2),[1] is reporting worldwide more than 500 million cases of Coronavirus disease 2019 (COVID-19). Among general population, an increased risk of severe infection or death is due to age, sex and comorbidities such as hypertension, chronic cardiovascular and pulmonary disease, diabetes, immunodeficiency[2–4] and cancer.[5,6] Patients with haematological malignancies represent a vulnerable population, since the underlying disease and the treatments they receive make them highly immunocompromised. COVID-19 infection in these patients exhibit a more severe disease course and higher mortality rates ranging from 30% to 40% according to different reports.[7–10]

Patients with lymphoma are a subgroup characterized by hypogammaglobulinemia and dysfunction of B and T-cells which are crucial in the innate and adaptive immune response to viral pathogens. However, the contribution of either patient-related, or disease-related, or therapy-related risk factors on the outcome needs to be better defined. Mortality rate in this group of patients is about 32%–35% according to the reports inherent to data of the first year of pandemic.[11,12]

Various therapeutic and prophylactic agents are being used against COVID-19 such as antiviral drugs, vaccines and, lately, monoclonal antibodies neutralizing SARS-CoV-2 by binding to the viral S-protein (Anti-S MoAbs).[13–16] Anti-S MoAbs have been approved by Regulatory Agencies for the treatment of mild/moderate COVID-19 in high-risk patients, following the results of clinical trials showing their feasibility and usefulness in reducing severity and death-rate[9] of COVID-19 infection[−11].

In this setting, our purpose was to report our monocentric real-life experience with patients affected by lymphoma and COVID-19 along 2 years of pandemic and to evaluate the overall mortality, the impact of anti-COVID treatment on the infection, and haematological disease-related outcome.

2 | METHODS

This retrospective monocentric cohort study included all patients affected by lymphoma and followed at Policlinico Umberto I, Sapienza University of Rome, who received a diagnosis of SARS-CoV-2 infection from 10 March 2020 to 31 March 2022. Demographics, clinical and biological characteristics were collected through revision of clinical files. This study was approved by the internal review board and respects the principles of declaration of Helsinki. Diagnosis of SARS-CoV-2 infection was performed with Reverse Transcription Polymerase Chain Reaction (RT-PCR) on nasal swab. As well RT-PCR was employed to determine the end of infection. All patients received the standard of care in force at the time of infection according to COVID-19 Treatment Guidelines Panel's and Agenzia italiana del farmaco (AIFA) recommendations. Vaccination was strongly recommended to all patients since February 2021. Anti-S MoAbs were administered to all outpatients with mild to moderate symptoms as soon as possible. Infection course and COVID19 severity were monitored as the presence of CT-documented pneumonia, requirement of hospitalization and oxygen therapy. Major comorbidities were registered.[2,4–6] Patients with identifiable haematological disease at the time of infection or receiving induction therapy, were considered as carriers of active haematological disease.

Primary objective was to evaluate in patients affected by lymphoma and COVID19 infection the overall mortality, the impact of anti-COVID treatment on the infection- and haematological disease-related outcome. Secondary objectives were: to determine which clinical features could affect the prognosis of these patients, which parameters of severity of infection were associated with increased risk of death and to evaluate the impact of anti-COVID vaccination.

Patients were compared according to the period of infection (different waves) and to anti-COVID MoAbs employment in terms of progression of infection registered as occurrence of pneumonia, hospitalization, oxygen therapy, overall and COVID-related death rate and infection duration, determined as days between the first positive nasal swab and the first negative nasal swab.

Statistical analysis was performed using IBM software SPSS statistics v.25.

Descriptive statistics, arepresented for normally distributed variables. To compare differences between the groups, univariate logistic regression was used to evaluate potential risk factors associated to death or to severe COVID19 infection. The χ^2 test was used for categorical variables, Mann-Whitney *U*-test for continuous variables. The odds ratio (OR) for each independent variable was determined with a confidence interval (CI) of 95%. Kaplan-Meier curves were also employed to assess difference in terms of overall survival (OS), considered as time range between diagnosis of infection and death without negativity at RT-PCR. A multivariate analysis was performed with selected variables, both infection-independent and infection-dependent that were significant in the univariate analysis ($p < 0.05$), using COX regression model when appropriate with 1 grade of freedom.

3 | RESULTS

3.1 | Cohort

One-hundred-seventy-six patients, consecutively observed between March 2020 and March 2022 were included. The characteristics of the population and hematologic features are reported in Table 1. Overall, 23 deaths were registered (overall mortality 13.1%), 2 deaths were attributed to disease progression during infection, median time to death from first positive swab was 17 days (range 5–29). Median days of follow-up at 15 June 2022 were 106 (range 67–788).

The comparison between cohort 1 including patients with COVID-19 infection during the first pandemic waves (March 2020 – August 2021), and cohort 2, during the last pandemic wave (September 2021 – March 2022), did not evidence significant differences in characteristic's distribution except for: disease status, in

TABLE 1 Characteristics of the whole population and considering period of infection

Features		Cohort 1 March 2020-August 2021		Cohort 2 September 2021-March 2022		Overall population		
		N (70)	%/st.dv. of first waves	*N* (106)	%/st.dv. of last wave	*N* (176)	%/st.dv. of total	*p* value
Sex	Male	36	51.4%	64	60.4%	100	56.8%	0.24
	Female	34	48.6%	42	39.6%	76	43.2%	
Age for range	18–64	31	43.8%	61	58.1%	92	52.3%	0.059
	65–95	39	56.5%	45	42%	84	47.7%	
Age years	Median (st.dv.)	66	(16.99)	61	(17.06)	61.5	(17.09)	0.11
Comorbidity	Yes	29	56.9%	40	43%	69	47.9%	0.11
	No	22	43.1%	53	57%	75	52.1%	
Comorbidity index	Median (st.dv.)	1	(1.8)	1	(8)	1	(6.4)	0.055
Other malignancies	No	55	88.7%	86	91.5%	141	90.4%	
	Previous malignancy	6	9.7%	7	7.4%	13	8.3%	0.84
	Other active malignancies	1	1.6%	1	1.1%	2	1.3%	
Active disease	Staging/Induction	23	34.8%	51	48.6%	74	43.3%	0.001
	Undergoing maintenance	3	4.5%	18	17.1%	21	12.3%	
Patients in follow-up		40	60.6%	36	34.3%	76	44.4%	
Lymphoma subtype	B-NHL	59	84.3%	85	81.0%	144	82.3%	0.53
	HD	10	14.3%	15	14.3%	25	14.3%	
	T-NHL	2	1.8%	5	4.8%	7	3.4%	
Disease	FL	17	24.3%	26	24.5%	43	24.4%	0.007
	DLBCL	5	7.1%	19	17.9%	24	13.6%	
	HL	8	11.4%	14	13.2%	22	12.5%	
	SLL	12	17.1%	6	5.7%	18	10.2%	
	Indolent B NHL no FL	23	32.9%	19	17.9%	42	23.9%	
	MCL	1	1.4%	12	11.3%	13	7.4%	
	T-NHL	2	2.9%	5	4.7%	7	4.0%	
	PMBCL	0	0.0%	3	2.8%	3	1.7%	
	HGBL	2	2.9%	2	1.9%	4	2.3%	
Transplant	Yes	4	5.9%	9	8.8%	13	7.6%	0.49
	No	64	94.1%	93	91.2%	157	92.4%	
Last therapy performed	None	7	10.0%	7	6.6%	14	8.0%	0.59
	Chemotherapy	15	21.4%	20	18.9%	35	19.9%	
	Bendamustine containing regimen	11	6.25%	18	10.22%	29	11.4%	
	R-chemotherapy	23	13.0%	31	17.6%	54	35.8%	
	Chemo-free regimen	14	20.0%	29	27.4%	43	24.4%	
	CAR-t	0	0.0%	1	0.9%	1	0.6%	
Number of treatment lines	0	25	35.7%	25	23.6%	50	28.4%	0.24
	1	37	52.9%	57	53.8%	94	53.4%	
	2	3	4.3%	14	13.2%	17	9.7%	

(Continues)

TABLE 1 (Continued)

Features		Cohort 1 March 2020-August 2021 N (70)	%/st.dv. of first waves	Cohort 2 September 2021-March 2022 N (106)	%/st.dv. of last wave	Overall population N (176)	%/st.dv. of total	p value
	3	3	4.3%	5	4.7%	8	4.5%	
	4	2	2.9%	3	2.8%	5	2.8%	
	5	0	0.0%	1	0.9%	1	0.6%	
	6	0	0.0%	1	0.9%	1	0.6%	
Anti-CD20 MoAb exposure	No	25	36.8%	28	28.6%	53	31.9%	0.26
	Yes	43	63.2%	70	71.4%	113	68.1%	
At least 1 dose of vaccine administered	Yes	11	17.2%	94	94.0%	105	64.0%	0.001
	No	53	82.8%	6	6.0%	59	36.0%	
SARS-CoV-2 Ab test	Not assessed	58	82.8%	68	64.15%	126	71.6%	0.006
	Positive	7	10.0%	15	14.2%	22	12.5%	
	Negative	5	7.1%	23	21.7%	28	15.9%	
Hypogammaglobulinemia	No	32	59.3%	37	43.5%	69	49.6%	0.071
	Yes	22	40.7%	48	56.5%	70	50.4%	
Days of follow-up from nasal swab	Median (range)	401	(261–788)	101	(67–250)	106	(67–788)	0.001

Note: In Table 1 are reported clinical baseline characteristics pre COVID19 infection of the whole cohort, expressed as total and divided according to the wave of infection from 10 March 2020 to 31 August 2021 (Cohort 1) versus 1 September 2021 to 30 March 2022 (Cohort 2). X^2 test, and Mann-Whitney *U* test were employed to assess significant differences in distribution. Not all data were available for every patient.

Abbreviations: Ab, Antibody; B-NHL, B-cell Non-Hodgkin Lymphoma; DLBCL, Diffuse Large B Cell Lymphoma; FL, Follicular Lymphoma; HL, Hodgkin Lymphoma; MCL, Mantle cell Lymphoma; MoAb, Monoclonal Antibody; N, number; PMBCL, Primary Mediastinal B-Cell Lymphoma; SLL, Small lymphocytic lymphoma; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; std, Standard deviation; T-NHL, T-cell Non-Hodgkin Lymphoma.

cohort 1 60% of patients were on follow-up at the time of infection against 34% in cohort 2; vaccination, overall, 64% ($N = 105$) of patients received at least one dose, 17.2% and 94% of cohort 1 and 2, respectively, 56 (31.8%) had received 3 doses at time of infection. We observed a significant reduction of COVID19-related symptoms at onset (79.8% vs. 91.9% *p* 0.039), CT-documented pneumonia (26.6% vs. 42.2%, *p* 0.028), rate of patients requiring oxygen therapy for COVID-19 infection progression (18.8% vs. 40.6%, *p* 0.006), median days of infection duration (19 vs. 26 days, *p* 0.002) in cohort 2 compared to cohort 1. A trend towards decreasing death rate was observed between cohort 2 and 1 (9.4% vs. 18.5%, *p* 0.076).

3.2 | Treatment of SARS-CoV-2

Antiviral treatment was administered to 58.7% of patients ($n = 93$): 41.3% ($n = 66$) received Anti-S MoAbs, of which 42 received sotrovimab and 18 bamlanivimab/etesevimab while 6 casirivimab/imdevimab; 23.1% ($n = 34$) received antiviral drugs: 13 received remdesevir, 9 received paxlovid and 5 molnupinavir; 7 patients received antiviral agents together with COVID MoAbs. Immune plasma was employed in associations with Anti-S MoAbs in 3 cases. Median time to Anti-S MoAbs administration was 4 days (SD 4) from the first positive nasal swab. In Table 2, the characteristics of patients who received Anti-S MoAbs ($n = 66$) versus patients who did not ($n = 110$) are compared. Also, in these subgroups, there was no significant difference in characteristics 'distribution except for vaccination and mean days of follow-up (Table 2).

3.3 | Impact of Anti-S MoAbs on COVID infection

Patients were compared according to the employment of Anti-S MoAbs in terms of severity of SARS-CoV-2 infection and mortality (Table 2). Employment of Anti-S MoAbs showed a reduced risk of escalating severity of infection in terms of CT-documented pneumonia (26.2% vs. 35%, *p* 0.005) and requirement of oxygen therapy (14.5% vs. 31%, OR 0.52 range 0.28–0.93, *p* 0.003). Patients receiving MoAbs had a significantly lower risk of death (OS 93.2% vs. 82.7%, OR 0.72 range 0.57–0.9, *p* 0.025), this data was independent from vaccination status (Table 2). Moreover, patients with haematological active disease at the time of infection had major benefit from Anti-S

TABLE 2 Patients and COVID19 infection characteristics and severity at time of infection, reported comparing patients that received anti SARS-CoV-2 Monoclonal antibodies versus patients who did not

		COVID MoABs employed		COVID MoABs not employed		Total		
		N/Mean 66	%/SD	N/Mean 110	%/SD	N/Mean 176	%/SD	*p*
Sex	Male	40	60.6%	59	53.6%	100	56.8%	0.52
	Female	26	39.4%	50	46.4%	76	43.2%	
Age for range	18–64	38	57.6%	54	49.1%	92	52.3%	0.27
	65–95	29	42.4%	55	50.9%	84	47.7%	
Disease	Indolent B lymphoma	32	51.6%	68	62.7%	100	56.81%	0.29
	Aggressive B lymphoma	21	31.7%	23	20.8%	44	25%	
	HL	10	12.1%	15	12.7%	25	14.3%	
	T-NHL	3	4.5%	4	3.6%	7	3.4%	
Active hematological disease	Yes	32	48.5%	45	40.9%	77	43.75%	0.32
	No	34	51.5%	65	59.1%	99	56.25	
Comorbidities	No comorbidities	33	58.9%	42	47.7%	75	52.1%	0.19
	At least 1	23	41.1%	46	52.3%	69	47.9%	
Diabetes	Yes	5	7.7%	11	10.3%	16	9.09%	0.58
Obesity	Yes	4	6.3%	6	5.8%	10	5.68%	0.85
Previous transplant	Yes	6	9.5%	8	7.5%	14	7.95%	0.42
Hypogammaglobulinemia	Yes	29	54.7%	41	47.7%	70	39.7%	0.42
Lymphocytes at time of infection	n/mmc	1461	1015	1853	2016	1657	1515	0.19
Lymphopenia at time of infection	>1500	34	51.5%	65	60.2%	99	56.9%	0.26
	≤1500	32	48.5%	43	39.8%	75	43.1%	
MoAb anti-CD20 exposure	No	16	26.2%	37	35.2%	53	31.9%	0.23
	Yes	45	73.8%	68	64.8%	113	68.1%	
Bendamustine in the current or last regimen	Yes	12	18.2%	17	15.6%	29	16.47%	0.65
Vaccination	Yes	60	90.91%	45	45.0%	105		0.001
	No	6	9.09%	55	55.0%	61		
COVID19 onset								
Symptoms	Yes	49	80.3%	87	87.0%	136	84.5%	0.25
	No	12	19.7%	13	13.0%	25	15.5%	
Fever	Yes	40	65.6%	72	72.7%	112	70.0%	0.33
Coughing	Yes	30	49.2%	49	50.0%	79	49.7%	0.92
Pharyngodynia	Yes	13	21.7%	19	20.4%	32	20.9%	0.71
COVID19 escalation								
Pneumonia documented	Yes	16	26.2%	35	37.2%	51	32.9%	0.005
	No	32	52.5%	25	26.6%	57	36.8%	
	NA	13	21.3%	34	36.2%	47	30.3%	
Other antiviral agents employed	Yes	8	13.3%	26	29.9%	34	23.1%	0.04
	No	52	86.7%	61	70.1%	113	76.9%	
Oxygen support	No	53	85.5%	63	64.3%	116	72.5%	0.003

(Continues)

TABLE 2 (Continued)

		COVID MoABs employed		COVID MoABs not employed		Total		
		N/Mean 66	%/SD	N/Mean 110	%/SD	N/Mean 176	%/SD	p
	Yes	9	14.5%	35	35.7%	44	27.5%	
Hospitalization	No	51	77.2%	55	56.1%	106	64.6%	0.073
	Yes	15	26.8%	43	43.9%	58	37.7%	
Time of hospitalization	Days	11	11	22	19	19	18	0.042
Progression of disease during infection	Yes	2	3.8%	5	6.9%	7	5.6%	0.46
Time of positivity	Days	24	23.7	25	13	24.7	18.4	0.77
Follow-up from nasal swab	Days	52	60	190	201			0.001
Treatment delayed	Yes	28	54.9%	31	37.3%	59	44.0%	0.06
Therapeutic scheme changed	Yes	12	23.5%	11	13.6%	23	17.4%	0.15
Status	Alive	62	93.9%	91	82.7%	153	86.9%	0.025
	Dead	4	6.1%	19	17.3%	23	13.1%	

Note: Patients characteristics reported comparing subjects who received anti SARS-CoV-2 Monoclonal antibodies versus subjects who did not. $\chi 2$ test, and Mann-Whitney *U* test were employed to assess significant differences in distribution. Not all data were available for every patient.

Abbreviations: B-NHL, B-cell Non-Hodgkin Lymphoma; HL, Hodgkin Lymphoma; N, number; std, Standard deviation; T-NHL, T-cell Non-Hodgkin Lymphoma.

MoAbs employment, with an OS rate of 90.6% (29/32) opposed 78.2% (32/45) for patients who did not (Figure 1, *p* 0.033). Overall, we observed 4 deaths on 66 patients receiving anti-S MoAbs (6.1%). No death was reported among the 42 patients who received sotrovimab. No Grade 3–4 infusion-related complications were reported.

3.4 | Death risk factors

Risk-factors showing a significant association with death are reported in Figure 2. Among patient-related risk factors, age above 65, having at least 1 comorbidity, diabetes and obesity, resulted significantly associated with an unfavourable outcome (Figure 2).

Among lymphoma-related risk factors, previous exposure to bendamustine (OS 64%, 10/29 vs. 91% 13/147, *p* 0.0001) (Figure 3A) and active disease at the time of infection (OS 77% vs. 92% *p* 0.002) (Figure 3B) resulted significantly associated with worst outcome; bendamustine increased death-risk was independent from anti-CD20 exposure (Figure 2). Patients with progression of lymphoma during COVID19 infection and those who delayed haematological treatment for the infection had a significantly lower OS, 60% (*p* 0.001) and 80% (*p* 0.002), respectively, compared to the other patient population. No survival difference was observed regarding histology subtype, employment of rituximab, obinutuzumab or immune modulators. Neither hypogammaglobulinemia, previous transplant, or number of previous lines. Instead, hypogammaglobulinemia showed an augmented risk of pneumonia (40.3% 25/62 vs. 21% 13/61, *p* 0.0001).

Regarding COVID19 severity factors, documented pneumonia, hospitalization requirement (OS 59% 34/58, vs. 97% 103/106, *p* 0.0001) (Supplementary material, Figure S4 A), and oxygen support therapy (OS 56%, 25/44 vs. 97%, 112/116, *p* 0.0002) (Supplementary material, Figure S4 B) were strongly associated with impaired survival.

Multivariate analysis was performed in three steps applying Cox Regression model: firstly, when all factors significant in univariate analysis were included in the Cox regression model, active disease, comorbidity, oxygen therapy, documented pneumonia and hospitalization resulted independent predictors of survival. Secondly, risk-factors independent from COVID infection were included: presence of at least 1 comorbidity, of active lymphoma undergoing treatment and previous bendamustine exposure were all confirmed as negative impact factors on survival. Multivariate analysis including only features of COVID 19 severity showed that oxygen therapy and hospitalization carried the highest impact on infection outcome (Table 3).

3.5 | Impact of vaccination and other anti-COVID therapies

Death rate was 10.5% among vaccinated patients and 13.6% for unvaccinated (*p* 0.54). Patients receiving at least one dose of vaccine showed a significantly lower incidence of fever (61.4% vs. 84.2%, OR 0.69 range 0.56–0.85, *p* 0.002), of manifest symptoms (79.2% vs. 93%, OR 0.71 range 0.57–0.91, *p* 0.017), of CT-documented pneumonia (29% vs. 41%, *p* 0.04) and of oxygen support requirement

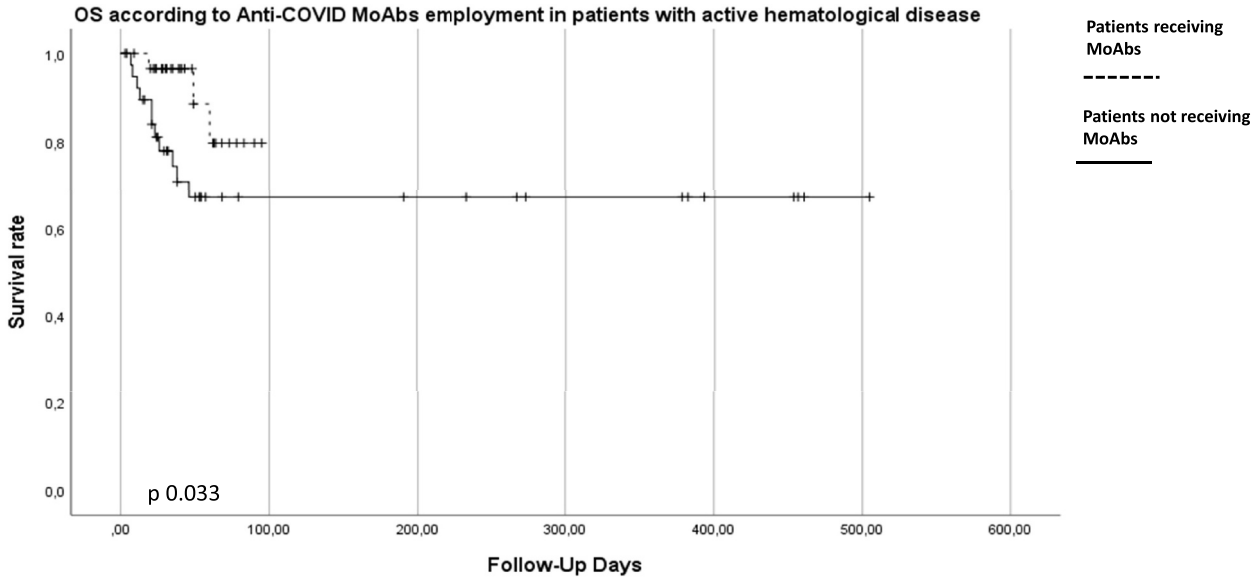

FIGURE 1 Overall survival (OS) according to Anti-COVID MoAbs employment in patients with active hematological disease. OS in patients with active disease or undergoing maintenance who received anti-SARS-CoV-2 monoclonal antibodies versus patients who did not. Univariate analysis was performed with Kaplan-Meier curve. Patients receiving anti-SARS-CoV-2 monoclonal antibodies showed significant benefit in terms of survival when active disease was present at time of the infection.

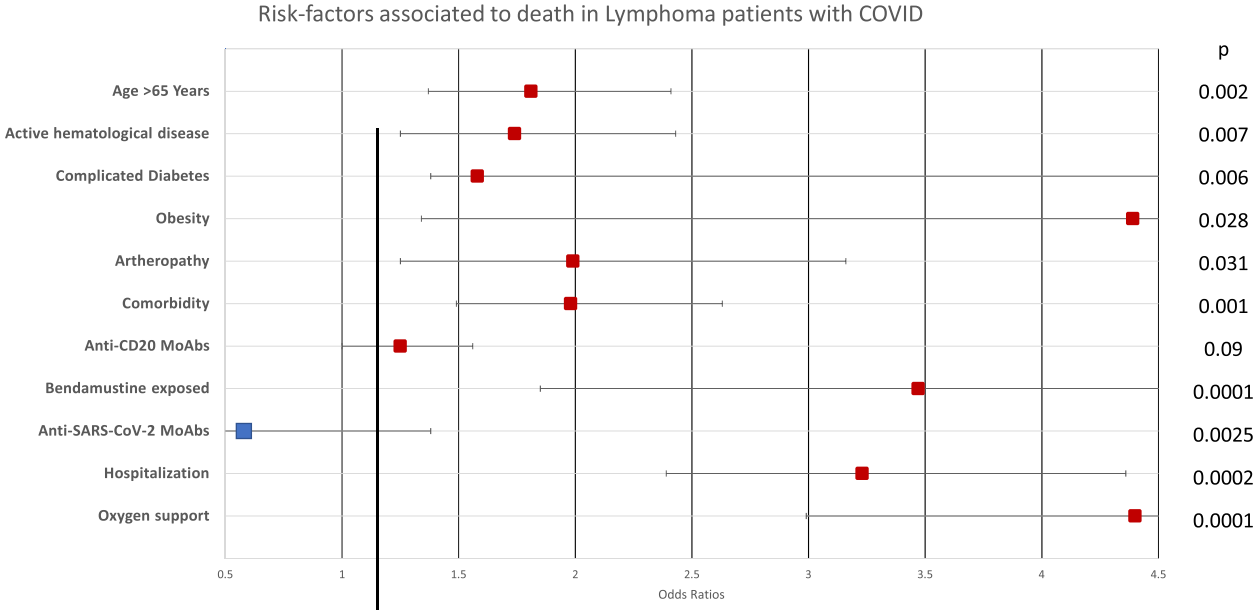

FIGURE 2 Death risk factors in univariate analysis. The odds ratio (OR) of single factors associated to death risk and relative *p*-value of univariate analysis (χ^2 test). While the employment of anti-SARS-CoV-2 monoclonal antibodies brings benefit in terms of overall survival (OS). Comorbidities, Bendamustine, and infection severity had a negative impact on the prognosis of COVID19 in Lymphoma patients.

(19.2% vs. 39.7%, OR 0.65 range 0.45–0.92, *p* 0.005). Fifty of 176 (28.4%) patients were tested for IgG anti-spike antibodies that were detected in 22 (44%); the comparison with patients tested that did not develop antibodies did not evidence survival benefit. The median number of days of infection were lower in vaccinated patients (19.5 VS 25.5 *p* 0.015).

In particular, among patients who received 3 doses of vaccine (*n* = 56, 31.8%), the employment of anti-COVID MoAbs showed a trend of superior survival (OS rate 97.3% 36/37 vs. 84.2% 16/19) respect to patients who did not receive Anti-S MoAbs (*p* 0.064).

Neither significant survival differences nor clinical benefit on COVID19 severity were evidenced in the whole cohort for patients receiving other antiviral agents. Seven patients received antiviral agents together with COVID MoAbs with no significant difference in the outcome, death rate was 14.7% (5/34) versus 12.6% (18/142) in patients not receiving oral antiviral drugs (*p* 0.55).

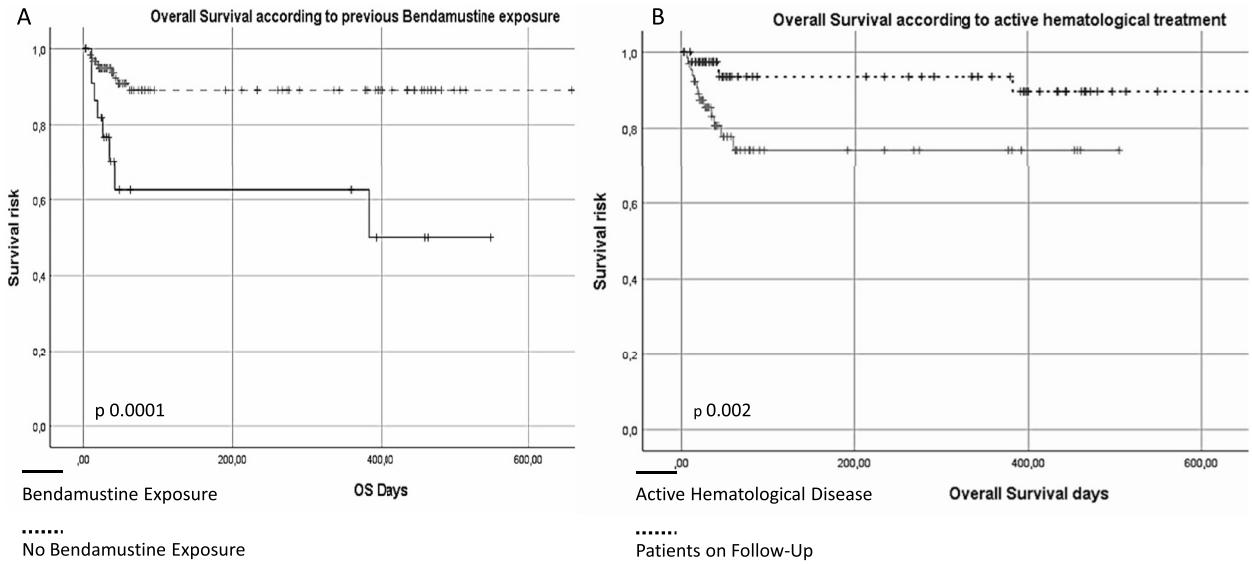

FIGURE 3 Overall survival (OS) according to Bendamustine exposure (A) and to active hematological disease (B). OS in the whole cohort according to Bendamustine exposure in the last or current treatment (A) and presence of active disease receiving treatment or maintenance against patients achieving remission in follow-up (B), showed a significant impact on survival in patients affected by Lymphoma with COVID19 infection. Univariate analysis was performed with Kaplan-Meier curves.

TABLE 3 Multivariate analysis

	Univariate analysis	Multivariate analysis all factors included		Multivariate analysis Infection independent risk factors		Multivariate analysis Infection-related risk factors	
	p	HR (CI 95%)	*p*	HR (CI 95%)	*p*	HR (CI 95%)	*p*
Age >65 years	0.002	1.48 (0.26–8.21)	0.7	2.54 (0.69–9.36)	0.140	/	/
Active disease	0.007	8.95 (1.05–76.29)	0.045	**2.49 (1.00-6.41)**	**0.05**	/	/
Diabetes	0.006	3.12 (0.65–14.8)	0.15	2.22 (0.53–9.21	0.123	/	/
Obesity	0.028	0.99 (0.18–5.44)	0.9	2.55 (0.77–8.42)	0.087	/	/
Artheropathy	0.031	9.26 (0.92–100)		0.68 (0.68–2.30)	0.46	/	/
Comorbidity	0.001	10.15 (1.33–77)	0.026	**6.53 (1.88-22.60)**	**0.003**	/	/
Anti-CD20 MoAbs	0.09	5.99 (0.62–57)	0.12	1.48 (0.37–5.86)	0.57	/	/
Bendamustine exposure	0.0001	1.19 (0.27–5.14)	0.81	**4.2 (1.69-10.45)**	**0.002**	/	/
Anti-SARS-CoV-2 MoAbs	0.0025	0.85 (0.3–2.9)	0.7	/	/	0.85 (0.3–2.9)	0.7
CT documented pneumonia	0.004	3.52 (1.032–12)	0.044	/	/	1.84 (0.78-0.32)	0.15
Hospitalization requirement	0.0002	16.36 (2.93–138)	0.013	/	/	**13.3 (1.45-123)**	**0.022**
Oxygen therapy requirement	0.0001	10.31 (0.96–110)	0.054	/	/	**3.84 (1.01-15.03)**	**0.049**

Note: Multivariate analysis was performed in three steps applying Cox Regression model: starting from univariate analysis *p*-value all significant factors were included in Cox regression model evidencing comorbidity, oxygen therapy and hospitalization as independent predictors of survival. Afterwards , risk-factors independent from COVID infection were included: presence of at least 1 comorbidity, presence of active disease undergoing treatment and previous bendamustine exposure were all confirmed as negative impact factors on survival. Multivariate analysis including only features of COVID 19 severity showed that oxygen therapy and hospitalization carried highest impact on infection outcome. In bold: Statistically significant values.

Abbreviations: CI, Confidence Interval; CT, Computed Tomography; HR, Hazard Ratio; MoAbs, Monoclonal Antibodies; y, Years.

4 | DISCUSSION

We present a monocentric cohort of patients affected by lymphoma, who have been receiving diagnosis of SARS-CoV2 infection throughout the COVID-19 pandemic in Italy. All the patients were outpatients and paucisymptomatic at the onset of infection. We observed a time-related decreasing trend of death rate from 18.5% in Cohort 1 (March 2020- August 2021) to 9.4% in Cohort 2 (September 2021-March 2022). Our overall mortality is lower than other rates reported in literature,[7–10,17] even in the cohort 1. This

could be explained by the higher number of patients without active disease at time of infection, that we highlighted as unfavorable predictive factor for mortality (Table 1).

As of June 2022, a significant reduction of COVID-19 severity has been achieved worldwide, compared with the higher mortality rate registered during first and second waves,[7,18–21] justified by several factors including, as well, the spread of SARS-CoV2 genome variants that seem to have a reduced virulence.[19–22]

Nevertheless, hematologic patients diagnosed with COVID-19 continue to be considered a high-risk category due to impaired or dysfunctional adaptive immune response. COVID-19 in lymphoproliferative diseases can compromise clinical outcome and hematologic treatment administration. For this reason, new anti-SARS-CoV2 therapeutics can be precious tools in order to ultimately decrease mortality rate and shorten the time to cancer treatment resumption.

Our series included 66 patients undergoing anti-S MoAb, alone or in combination with other antiviral drugs, administered at a median time of 4 days from the positive test, representing to our knowledge the largest group of lymphoma patients who have received anti-S MoAbs. The choice of the specific compound was based on local availability, national approval and the epidemiology of circulating SARS-CoV2 variants, however genomic variants of SARS-Cov2 were not analyzed at our hospital.

In our study, the comparison of clinical outcome between patients who underwent monoclonal therapy and patient who did not, showed a reduction in infection complication rates, reducing time of hospitalization, altogether leading to a significant mortality rate reduction that stands at 6.1%. However, we have to consider that the majority of patients of this subgroup were vaccinated, which also in our experience proved to reduce the respiratory complications COVID-19 related.

To date, available literature shows an overall mortality decrease concordantly with our findings: Weinbergerovà and colleagues[23] recently analyzed 88 onco-hematologic patients affected by COVID-19 undergoing therapy randomly with bamlanivimab, or casirivimab/indevimab, compared with a control cohort who did not undergo any COVID-19 treatment. The study included 30 patients affected by lymphoma and, in line with ours, demonstrated a death rate reduction for patients treated with anti-S MoAbs compared with those not-receiving anti-S MoAbs (7% vs. 19%, respectively).[23] A US single center observational study analyzed the outcome of 42 cancer patients treated with either bamlanivimab or casirivimab/indevimab for COVID-19 with a median time of 5 days from symptoms onset.[18] The study included 32 hematologic patients, of which only 1 patient died in ICU setting for the progression of a diffuse large B cell lymphoma during COVID-19 infection.[18] In this experience, extremely low mortality could be related to sample size and shorter follow-up of 30 days, as compared with our study.

The majority of published data showed the efficacy of new antiviral drugs also in hematologic cohorts, nevertheless these drugs were administered only in 34 patients of our cohort 2, without a significant benefit.[13,24–26] The small number of treated patients makes our findings not suitable for a more thorough analysis.

Multivariate analysis evaluated which variables could affect the efficacy of monoclonal therapy, increasing the risk of severe COVID-19 and death in our cohort. General comorbidities such as diabetes, obesity, cardiovascular disease, which are well known risk factors in the general population together with age were confirmed as well in lymphoma patients.[7,17,26]

Moreover, our study shed light on several lymphoma-related features: patients with previous exposure to bendamustine, regardless of lymphoma subtype, number of previous therapy lines, association with anti-CD20 antibodies, showed the worst outcome. Despite bendamustine-related B- and T-cell prolonged suppression was well known, and bendamustine replacement with different chemotherapy schemas was hypothesized at start of pandemic,[26] to our knowledge, this is the first real-life experience with or without anti-CD20 MoAbs, whereas the major reports on COVID-19 outcome in lymphoma cohorts did not find significant variance among different therapy regimens.[11,17,26] In consideration of certain clinical settings where bendamustine is recommended and not replaceable with therapeutic confidence, patients undergoing bendamustine containing regimens are at high-risk of developing severe COVID19 infection. For these patients anti-Covid measures should be enhanced and they could be candidates for the administration of anti-S- MoAbs as prophylaxis. Due to the high number of patients across the groups previously exposed to rituximab or obinutuzumab, and the well-known role of those drugs in impairing humoral vaccine responsiveness,[27] it is not feasible to postulate a clear association between COVID19 severity and anti-CD20 therapy.

Despite a significant association has been found between Hodgkin lymphoma and better prognosis in various reports,[11,17,26] no significant association was found with mortality on the base of histologic subtype, lymphopenia, number of prior lines and chemotherapy regimen other than bendamustine, in our series. Stem cell transplant recipients were 7.6% in our study and, in line with the published literature, this group did not show worse outcome.[28] As expected, patients with active hematologic disease or receiving treatment or maintenance at time of infection, are at high-risk of developing a serious infection, in this setting the employment of anti-S- MoAbs should be recommended, as shown by our data.

Vaccination brought a dramatic change in the infection outcome in the general population. However, in lymphoproliferative diseases its efficacy in preventing severe COVID19 infection is limited due to impaired immunity[29] (active disease status regardless histology subtype, anti-CD20-based regimens) compared to vaccinated controls.[30] Nevertheless, patients who completed vaccination schedule had most benefit from anti-S-MoAbs employment in our study. Based on our results, we can confirm that the vaccination is strongly recommended in this subset of patients.

Moreover, we found that the risk of developing severe infection with CT-documented pneumonia, need of hospitalization and oxygen support, were remarkably reduced in patients who underwent anti-S-MoAbs therapy and vaccinated. Unexpectedly hypogammaglobulinemia and lymphopenia did not result in an augmented death-risk, probably the impaired lymphocytes function given by disease and

anti-lymphoma treatment administration had major impact in this context.

Some of our findings differ with the results from other reports. Visco and colleagues designed an easy-to-consult prognostic model identifying predictors of death in lymphoma patients affected by COVID-19 such as age >65, platelet count <100 × 10^9/L, male sex and lymphocyte count <650/mmc.[17] This finding can be explained by the fact that cell-immunity in lymphoma is probably compromised by an impaired function not necessarily or not only reflected by a decreased count.

Concerning the EPICOVIDEHA survey which retrospectively analyzed risk-factors for severe COVID-19 in 3801 patients with hematologic malignancies, 1242 patients with lymphoma were the largest subgroup.[10] In multivariate analysis, even in a population with any type of hematologic neoplasm, active disease, comorbidities, smoking history and lymphopenia were the strongest variable associated with death-risk.[10] Comparing these results to those of our study, we observed some shared points with some differences that could be due to the inclusion of more waves of pandemics and the employment of antiviral drugs; smoking data were not registered in our series, instead presence of chronic obstructive pulmonary disease was regularly reported.

In our multivariate analysis, we highlighted additional factors impactful on prognosis at time of infection (infection-independent) and factors which during COVID-19 escalation could mostly affect prognosis (infection course-dependent). Covid-MoAb employment alone was not confirmed as an independent prognostic factor.

Major limitations of the present study are the retrospective analysis and the relatively small number of patients included. However, considering the study of a consistent and homogeneous population from a single center, we believe that our findings might represent a helpful tool for hematologists in decision-making in the clinical setting.

In the near future, SARS-COV-2 might not be the same issue for general health-care but it will still be spreading in the community and in hospitals and SARS-CoV-2 variants could furtherly modify the therapeutic landscape. In this scenario, the lymphoma patient undergoing induction therapy is still at high-risk of developing life-threatening SARs-CoV-2 infection. Hematologists will have to assess the risk for COVID-19 in every new patient, promptly recognize the infection and address anti-COVID compounds in order to complete life-saving treatment regimens.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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